

Outcomes when Switching from a pro re nata Regimen to a Treat and Extend Regimen Using Aflibercept in Neovascular Age-Related Macular Degeneration

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Keywords

Neovascular age-related macular degeneration · Intravitreal injections · Aflibercept · Pro re nata regimen · Treat and extend regimen

Abstract

Purpose: To investigate outcomes in patients with neovascular age-related macular degeneration (AMD) switched from a pro re nata regimen (PRN) to a treat and extend regimen (TER) under aflibercept. **Procedure:** Thirty-two patients were observed over 2 years: the first year on PRN and the second year on TER. Best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were evaluated. Intra- and subretinal fluid as well as the number of visits and injections were assessed. **Results:** Both regimens resulted in a stable BCVA. Patients in TER had a significant decrease of CRT after 1 year compared to 1 year of treatment on PRN ($p < 0.0001$). TER resulted in significantly less visits; however, significantly more injections were observed over the course of 1 year compared to PRN (10.25 vs. 7.5, $p < 0.0001$ and 5.97 vs. 7.5, $p = 0.0002$, respectively). **Conclusion:** A switch from PRN to TER in patients treated with aflibercept for AMD appears to be safe.

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Introduction

Antiangiogenic agents have revolutionized the treatment of wet age-related macular degeneration (AMD) in the last decades. However, the initial enthusiasm for this treatment has been dampened by the need of monthly injections to obtain good functional outcomes. To avoid the associated treatment burden for patients and related health care costs, alternative treatment regimens were developed to reduce the number of injections needed. Pro re nata (PRN) or treat as needed is one of the attempts to lower the number of injections while trying to obtain good functional outcomes in terms of best-corrected visual acuity (BCVA). Several studies, such as the CATT and the IVAN trials, showed that a PRN regimen required up to 50% fewer injections compared to a monthly regimen [1]; however, PRN was shown to lead to marginally inferior functional outcomes [2–4] and less reduction of central retinal thickness (CRT) compared to monthly injections [1]. One disadvantage for both, the PRN and for the monthly regimen is the need for monthly visits. A more recently introduced strategy to optimize the benefit:risk ratio is the treat and extend regimen (TER), which usually involves fixed treatment intervals until

clinical remission is seen in optical coherence tomography (OCT), followed by either extension or decrease of treatment intervals, depending on OCT results [5, 6]. Although there is a relative paucity of data on TER therapy, it has been adopted by the majority of AMD-treating physicians, mainly because it decreases the frequency of office visits while minimizing disease activity [1]. A recent study compared ranibizumab to bevacizumab using a treat and extend protocol and found a comparable visual acuity (VA) after 1 year of treatment when compared to other clinical trials with monthly treatment [7]. Moreover, patients with neovascular AMD and initially good visual function (20/40 or better) seem to show comparable treatment results under TER after 2 years [8].

However, there is little data on what to expect in real life when switching from PRN to TER. In our study, we compared functional and anatomical outcomes of patients under long-term therapy with anti-VEGF who have been switched from PRN to TER.

Methods

Study Design and Patients

This was a 2-year observational, retrospective study at a tertiary referral center.

Patients over 50 years of age with choroidal neovascularization due to AMD with at least 2 years of continuous treatment with aflibercept were included. Within those 2 years, they had at least 1 year of continuous anti-VEGF-therapy using PRN with aflibercept prior to the switch to TER, and they had at least 1 year of continuous treatment under TER. The baseline of analysis was defined as the time point when the switch from PRN to TER occurred.

Regimens

Pro re nata Regimen. Patients were seen on monthly intervals. However, as this was a retrospective study, some patients had longer intervals due to conflicting schedules. Disease activity was assessed based on OCT. When there was evidence of hemorrhage, subretinal fluid (SRF), or intraretinal fluid (IRF) based on OCT, retreatment was applied; otherwise the patient was scheduled to be seen 4 weeks later.

Treat and Extend Regimen. Patients were seen and treated according to a treat and extend scheme. Extension of intervals were based on signs of activity in OCT. Stability was defined as no IRF or SRF, in which case the retreatment interval was extended by 2 weeks. If there were signs of activity (hemorrhages, IRF, or SRF) the intervals were shortened by 1 week to a minimum of 4 weeks.

Study Procedures

Medical records of patients with CNV secondary to neovascular AMD were reviewed and analyzed retrospectively according to the above-defined criteria. Patients identified from the procedure logs at the Department of Ophthalmology, University Hospital Bern, between November 1, 2012 and July 1, 2015, were reviewed. Patients who underwent intraocular surgery other than

intravitreal injections were excluded. Ethics approval (KEK-No. 093/13) to conduct this study was obtained from the local ethics committee, and the study was performed in accordance with ICH-GCP guidelines. The need for written consent from each individual patient was waived because of the retrospective nature of the study.

BCVA and the assessment of IRF and SRF were performed by physicians. Distance BCVA was tested using ETDRS charts, and the BCVA letter score was collected. CRT was measured using Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany; Software version 5.3). Scans were acquired using an established protocol consisting of volume scans. For the volume scan of $20^\circ \times 20^\circ$, 49 frames spaced $121 \mu\text{m}$ and each consisting of 512 A-scans were acquired. The automated real time was set between 6 and 12 to reduce noise. The primary end point of the study was BCVA. Secondary end points were CRT, subretinal fluid and IRF, as well as the numbers of aflibercept injections and visits.

Statistical Analysis

Data were collected in tables and statistical analysis was performed using the Prism GraphPad® commercial software package (Prism 6; GraphPad Software Inc., La Jolla, CA, USA). Data were analyzed using a paired *t* test. For all analyses, $p < 0.05$ was considered statistically significant. At each timeline, the different categories were tested for the mean value and standard deviation and compared to each other.

Results

General Data

Thirty-two patients met our inclusion criteria and were included in this retrospective study (24 female and 8 male patients). The mean age was 79.3 years (± 9.5 SD). All patients had received previous treatment with anti-VEGF agents and were on a long-term treatment course with anti-VEGF agents under PRN, with an average treatment time of 236.1 ± 95.3 weeks (or 4.5 years) prior to the switch from PRN to TER.

During the observation time, none of the patients under examination underwent cataract surgery.

Visual Acuity

During the first year of our study, patients on PRN treatment showed a stable VA (initial BCVA: 64.0 ± 15.2 ; end point BCVA: 64.0 ± 16.1). The mean change in VA was -0.52 letters in the PRN group and -0.65 letters in the TER group compared to baseline (Fig. 1).

CRT, IRF, and SRF

Patients after 1 year of TER treatment had a significant thinner retina (end point: $288 \pm 60 \mu\text{m}$) compared to 1 year of treatment using PRN (baseline: $330 \pm 89 \mu\text{m}$; initial CRT: $358 \pm 107 \mu\text{m}$) ($p < 0.0001$). The mean change

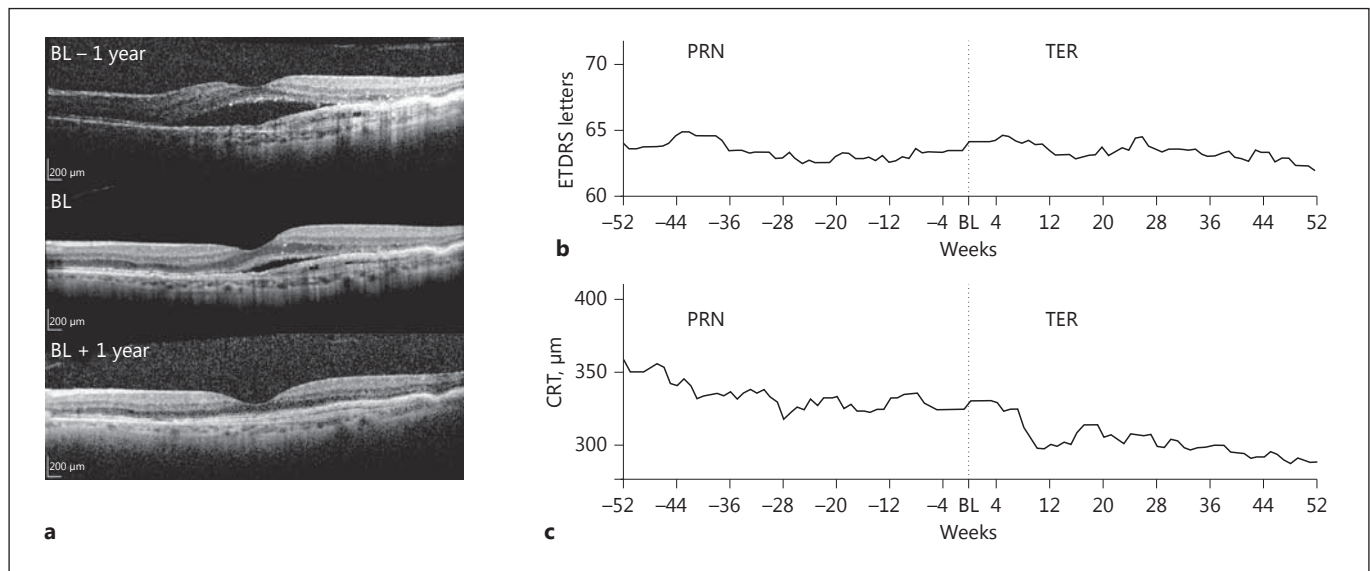


Fig. 1. a Representative OCT images at the beginning of PRN treatment (upper OCT image), at baseline, when the switch of treatment regimens took place (middle OCT image), and after 1 year of TER treatment (lower OCT image). **b, c** Development of BCVA (upper graph) and CRT (lower graph) over 2 years with a switch

of treatment regimen at baseline (BL). The values on the left side of the BL were recorded within the PRN; whereas on the right side of the BL, TER values are shown. OCT, optical coherence tomography; PRN, pro re nata regimen; TER, treat and extend regimen; CRT, central retinal thickness.

Table 1. OCT characteristics of patients who lost VA of more than 4 letters on the ETDRS chart

	PRN	TER
Patients who lost ≥ 4 letters on the ETDRS chart, n (%)	8 (25)	12 (37.5)
Gender, %		
Female	62.5	66.67
Male	37.5	33.33
Mean age, years	77.25	77.0
Increase of IRF, %	12.5	33.3
Increase of SRF, %	25	16.67
Increase of IRF and SRF, %	12.5	0
Increase of RPE atrophy, %	0	16.67
Increase of subretinal fibrosis, %	0	8.33
Opacification of refractive media, %	12.5	0
No differences/worsening in OCT to determine, %	37.5	25

PRN, pro re nata regimen; TER, treat and extend regimen; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, ocular coherence tomography; RPE, retinal pigment epithelium.

in CRT was 3.02 μm in the PRN group and -25 μm in the TER group compared to baseline.

IRF and SRF showed significant changes when switching to TER; both, the percentage of patients with IRF and/or SRF decreased when switching to TER. While 56% of the patients showed IRF at the beginning of the study (time

point: -52 weeks), 49% had IRF after 1 year of PRN (baseline), and 34% had IRF after 1 year of TER (+52 weeks, $p < 0.0001$). At the start of the observation period, 63% had SRF. After 1 year of treatment with PRN, the percentage of patients having SRF was unchanged and still at 62%, but was reduced to 50% after 1 year on TER ($p < 0.0001$).

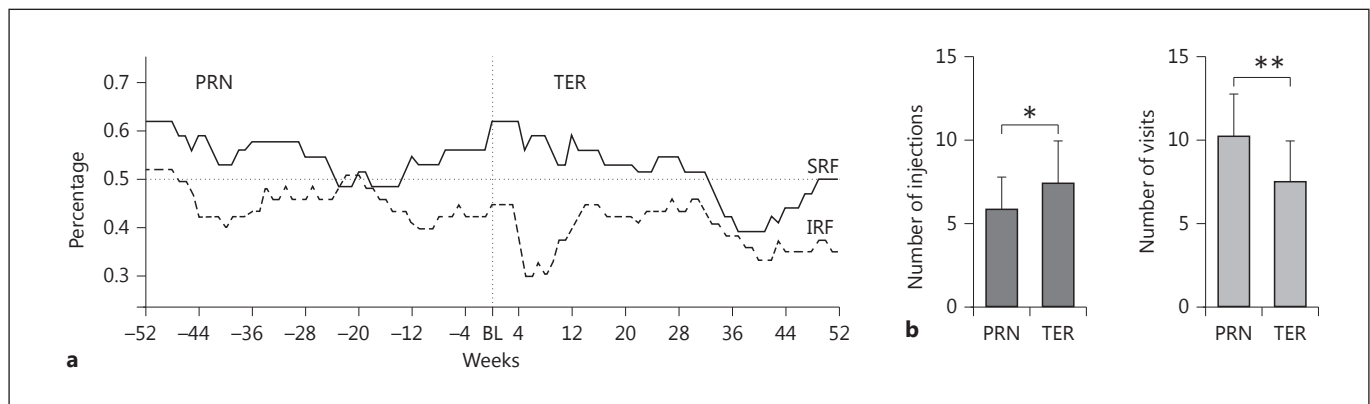


Fig. 2. a The percentage of patients having either SRF or IRF over the course of 2 years with a switch of treatment regimen from PRN to TER at baseline (BL) is shown. **b** Column graphs depicting the number of injections (black columns) and the number of visits

(grey columns) in the PRN and the TER group, respectively. SRF, subretinal fluid; IRF, intraretinal fluid; PRN, pro re nata regimen; TER, treat and extend regimen.

Subgroups of Patients Who Lost VA

Next, we investigated those patients who lost VA during the whole observational period (≥ 4 letters on the ETDRS reading chart). We identified 20 patients (8 patients during PRN and 12 patients during TER) and recorded the changes seen on OCT and slit-lamp exam of visits where VA dropped (Table 1).

Number of Injections and Visits

The total number of injections in the PRN timeline group was 5.97 ± 1.85 versus 7.5 ± 2.47 in the TER timeline group ($p = 0.0002$). The number of visits was 10.25 ± 2.59 in the PRN period versus 7.5 ± 2.51 in the TER period ($p < 0.0001$) (Fig. 2b).

Discussion

The results of our study show that patients being treated with aflibercept on PRN for 1 year and then being switched to TER recorded comparable visual outcomes. However, while the PRN group received fewer injections, the TER group underwent fewer visits and had a significantly decreased CRT after 1 year of treatment.

The change of VA in both regimen groups was similar. A marginal drop of approximately 2 ETDRS letters was seen in the TER period. This may be explained by the natural course of the disease as these patients had already been treated for an average of 2.5 years before being included into this study. Prunte et al. [9] performed a similar study in neovascular AMD patients receiving ranibizumab and evaluated the effect of switching from PRN to

TER in a clinical routine setting employing a similar TER protocol. Interestingly, with a similar mean treatment interval of 7.1 ± 2.3 weeks, they found a significant improvement of the Snellen BCVA after 1 year of TER (0.47 ± 0.22 to 0.55 ± 0.23), which is in contrast to our findings. This disagreement may be explained by divergent disease durations of the included patients or by the duration between the last injection on PRN and the first injection on TER.

Although the CRT decreased in the PRN period from 358 ± 106 to $330 \pm 89 \mu\text{m}$, CRT further decreased during the TER period. A recent retrospective study analyzing separately PRN and TER cohorts showed a similar decrease in CRT compared to baseline over a period of 3 years [10].

In our study, both the presence of IRF and SRF was significantly different in both treatment regimens. When treatment was switched from PRN to TER, patients showed less fluid in the TER arm (IRF 49 vs. 34%, SRF 63 vs. 50%). Fung et al. [11] found comparable results with 50% SRF and 50% IRF after 12 months of TER using 0.5 mg of intravitreal ranibizumab. Nevertheless, aside from our study, there are so far no systematic analyses on IRF and SRF during treatment with TER compared to PRN. However, the goal of TER is to achieve and maintain a “dry” macula by gradually increasing the length of time between injections in the absence of macular fluid [5, 10]; therefore, our findings underscore this principle.

Similar to the findings of other reports [10, 12], patients undergoing antiangiogenic therapy according to the TER dosing scheme received statistically more injections compared to PRN. The mean number of injections our patients received was 7.5 ± 2.47 in the TER compared

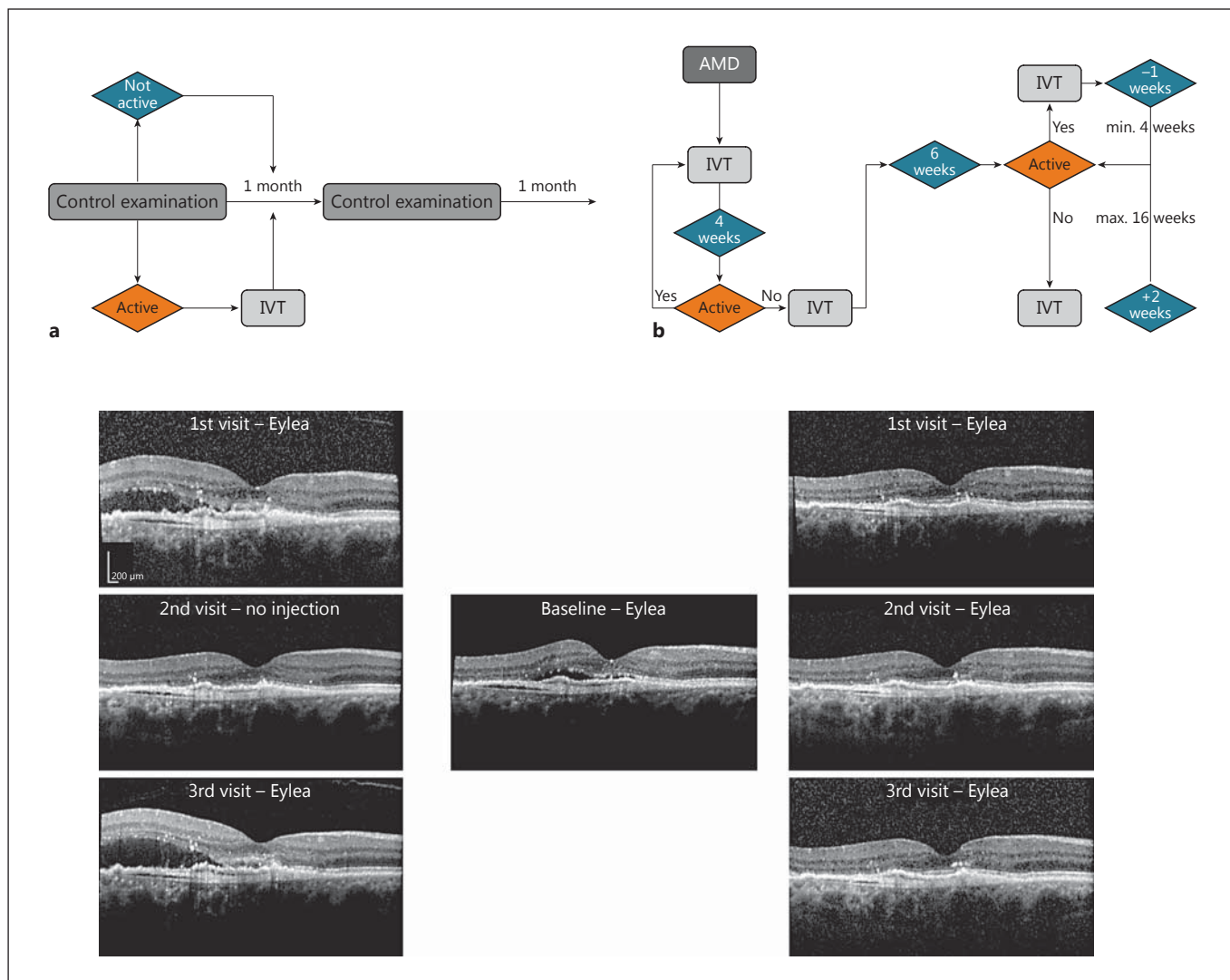


Fig. 3. a Flowchart of PRN treatment (top) and OCT images (bottom) acquired monthly during PRN treatment. An intravitreal injection of Eylea was carried out on every second month. The OCT image in the middle shows the baseline time point when the regimen was switched from PRN to TER. In total, the patient received 7 injections of Eylea and had 11 office visits during the year on PRN

treatment. The patient received 4 injections of Lucentis prior to the start of PRN with Eylea. **b** Flowchart of TER treatment (top) and OCT images on TER (bottom). In total, the patient received 9 injections of Eylea and had the same amount of office visits during that treatment regimen year. OCT, optical coherence tomography; PRN, pro re nata regimen; TER, treat and extend regimen.

to 5.97 ± 1.8 in the PRN. In 1 report, the difference of both groups was recorded as follows: 7.8 ± 1.3 injections in the TER versus 5.2 ± 1.9 injections in the PRN group [12]. Beside the so far mentioned papers, several other studies were conducted to evaluate the efficacy of TER in neovascular AMD using ranibizumab and bevacizumab [7, 13–16]. Different TER protocols were applied in respective studies but most of them increased the treatment intervals by 2 weeks per visit, unless evidence for disease activity was present. A recent literature review summarized

the so far conducted TER studies [17]. Based on these studies, a recommended TER algorithm was established, defining disease stability, disease activity, and addressing the extension interval. The consensus panel agreed on an extension interval of 2 weeks if neovascular AMD was stable. In cases of disease activity, the interval should be shortened by 1–2 week. In cases of severe disease activity, a re-induction of monthly treatment should be considered [17]. Our study employed the recommended TER algorithm and therefore gives valid insight into the poten-

tial benefit when switching from PRN to TER in a routine clinical setting (Fig. 3).

Our study bears several weaknesses, mainly due to its retrospective nature and the relatively low number of patients included. The retrospective design and the “real-world” setting led to visit intervals that were not strictly 4 weekly on PRN, resulting in fewer visits than expected. Generally, the follow-up intervals in TER were better adhered to compared to PRN. Maybe an interval of 4 weeks in the PRN group, as recommended, is not always easy to follow, as it may collide with holidays or other medical appointments in cases of other systemic diseases. Furthermore, because patients were switched from PRN to TER, there is likely to have been more disease progression in the period when TER was applied, which should be considered when assessing the characteristics associated with a significant VA loss under both treatment regimens. Nonetheless, we did not observe any severe recurrence, such as large subretinal bleeding, in between visits within the TER group.

In conclusion, our cohort showed no significant changes in BCVA when switched from PRN to TER. However, the CRT was significantly decreased and there were significantly less patients having IRF and/or SRF. In addition, significantly less visits were observed in the TER period, which may also arise from the fact that TER offers individualized and flexible treatment plans and intervals.

Disclosure Statement

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